CONFIDENTIAL

"Saturated fat intake and lung cancer risk among nonsmoking women in Missouri"

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Journal of the National Cancer Institute (1993), 85, 1906-1916

When presenting evidence to the EPA Scientific Advisory Board at their July 1992 open meeting, I (and others) put forward the argument that dietary factors could be important confounders of the modest association reported between spousal smoking and lung cancer. There were two bases for this argument. Firstly, there was evidence from a number of studies (including the UK Health and Lifestyle study for which I presented unpublished data) that nonsmokers married to smokers had "worse" diets than nonsmokers married to nonsmokers, with reduced consumption of fruit and vegetables and increased consumption of dietary fat. Secondly, there was abundant evidence of an association between risk of lung cancer and such "worse" diets, with numerous studies showing that fruit and vegetable consumption was negatively related to lung cancer (c.f. the review by Block and her colleagues - my review 670) and various studies noting a positive correlation with dietary fat (c.f. Goodman et al, 1992 - my review 650). Dr Samet of the EPA Scientific Advisory Board rejected my argument on the basis that it had not actually been properly demonstrated that diet affected risk in nonsmokers. Though I argued that it was incredibly implausible a priori that diet should only affect risk in smokers (if antioxidants in certain dietary components protect against

potential effects of carcinogens in tobacco smoke, why should they not protect against other carcinogens which presumably cause cancer in nonsmokers?). Dr Samet's arguments, among other reasons, led to the EPA arriving at the conclusion in their final report that diet did not cause a systematic bias in ETS/lung cancer studies.

Subsequent events have tended to confirm the view that the EPA were wrong. In the first place, the publication of the Block review on fruits and vegetables made it absolutely clear that there was a strong and consistent negative relationship. This conflicted with the EPA report which, on p5-56, stated that "the literature on the effect of diet on lung cancer is not consistent or conclusive, but taken altogether there may be a protective effect from a diet high in β-carotene, vegetables, and possibly fruits" (my underlining).

Secondly, a paper by Candelora et al in JNCI in 1992 (see my review 633), based on a Florida lung cancer case control study of nonsmoking women for which Stockwell et al (see my review 627) had previously reported a positive association of ETS with lung cancer, reported a striking variation in lung cancer risk in relation to various indices of diet. Thus individuals in the lowest quartile of vegetable consumption had an estimated five times greater risk of lung cancer (95% confidence interval 2-10) than those in the highest quartile, with significant trends also being noted in relation to consumption of green and yellow vegetables, fruits, total carotene, α-carotene, cryptoxanthin and

vitamin C. Dietary data related to usual intake over the past five years. On the Candelora data, vegetable consumption alone could explain over 60% of total observed lung cancer among nonsmokers.

In 1992, Brownson and his colleagues published a paper in the American Journal of Public Health reporting results from a large case-control study carried out in Missouri in 1986 to 1991. As I pointed out in my review 637, this study was based on a larger number of lung cancers in lifelong nonsmoking women, 431, than in any of the other 30-odd published studies of ETS and lung cancer, and found no relationship between lung cancer and any of the major indices of ETS exposure, with a relative risk of 1.0 (95% confidence limits 0.8-1.2) for marriage to a smoker. In that review I commented in detail on the design and statistical analysis of the study. Inter alia I pointed to a number of potential weaknesses and unusual features of the study:

(i) The cases were ill or dead, with some two-thirds of data coming from next-of-kin, while the controls were presumably mainly healthy. The possibility of recall bias is present, though partly minimized by analysis adjusting for respondent (self, next-of-kin).

(ii) Unlike most US lung cancer/ETS case-control studies which required 100% histological confirmation, only some three-quarters of the cases were histologically verified.

(iii) There must be some doubts about the representativeness of the controls for at least two reasons:

(a) The controls aged less than 65 were selected from state drivers' licence files and those aged 65 to 84 were selected from a roster of Medicare participants, and it was not clear

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how many women did not qualify in this respect;

(b) The non-response rates, 5% for cases and 25% for controls, were very different, leading to the possibility of bias if responders and non-responders differ in relevant ways.

(iv) The proportion of squamous cell cancers in this study was quite low, markedly less than seen in other studies of lung cancer in nonsmokers.

(v) Failure to give any results from the consensus diagnosis of lung cancer carried out by the three pathologists.

The paper by Alavanja et al reviewed here is based on the same Missouri lung cancer case-control study used by Brownson and his colleagues. Whereas the Brownson analyses had been based on a total of 615 cases (431 lifelong nonsmokers and 184 long-term ex-smokers) this study was based on the somewhat smaller number of 429 cases (294 lifelong nonsmokers and 135 long-term ex-smokers) for which the subject or next-of-kin had completed a food frequency questionnaire. Numbers of controls were similarly lower, 1021 vs. 1400.

The main finding of the Alavanja et al paper was that saturated fat consumption was extremely strongly positively related to lung cancer risk. As shown in Table 6 of the paper, risk estimates increased steadily by quintile, with risk in the highest quintile 6.14 times higher than that in the lowest (1.0, base). The trend and increase in the highest quintile were both enormously significant, with the 95% confidence interval for the high/low comparison of 2.63-14.40 well away from 1.0. One can readily calculate from the data in Table 6 that if the whole

population had the risk of the lowest quintile the overall risk of lung cancer would reduce by a factor of 2.686, i.e. a proportion attributable risk (PAR) of 62.8%. The association with saturated fat was noted to be stronger for cases with adenocarcinoma than for cases with other or unknown cell types.

Table 6 also shows that there were independent relationships of risk with consumption of beans and peas (negative) and with consumption of citrus fruits and juices (positive), with about a two-fold risk difference between high and low frequency of consumption. According to these data, the PAR for bean and pea consumption is 14.1% and for citrus fruits and juices is 29.7%. These two associations were similarly evident for cases with adenocarcinoma and for other cases. No other dietary factors showed a significant independent relationship with risk.

Points to note about this paper (which is in general clearly written in a balanced and scientific way) are the following:

(i) The analyses took into account age, smoking history (lifelong nonsmoker, ex-smoker), presence of previous lung disease, interview type (subject, proxy) and total calories. The authors, who obviously conducted a fair amount of statistical analysis, presented evidence that the main findings were similarly evident when results were restricted only to subjects who provided self-reports of dietary intake.

(ii) Unfortunately, however, unlike in the Brownson paper, results were not presented separately for lifelong nonsmokers. Given that lifelong nonsmokers form a major part of the total cases, and

given the authors seemed to have conducted detailed enough analysis to have been likely to pick up a major interaction if it existed, it is probable that the associations reported with dietary variables would have been similarly evident in lifelong nonsmokers, but it would have been nice to see such analysis presented.

(iii) In interpreting results from dietary studies generally, there are two important considerations to take into account. In the first place there is likely to be considerable inaccuracy in classifying subjects according to dietary intake. This is particularly true when, as here, many respondents are ill or next-of-kin, dietary questions relate to four years previously, and questions relate to food frequency with no details collected on portion size. Random errors would of course tend to result in under-statement of associations of diet with lung cancer risk, though differences in ability to recall diet between cases and controls might lead to over- or under-statement of associations. In the second place, where one has a whole range of dietary variables to analyze it is highly likely that the strongest associations seen are over-estimates, due to chance. The first source of bias can partly be dealt with by conducting studies with more carefully quantified data, and the second can partly be dealt with by basing inferences on multiple studies.

(iv) It should be noted that the analyses are all adjusted for total calories, so that one is effectively comparing people who take a high or low proportion of their calories in different ways. This may not be the only important question. Total intake of dietary

carcinogens or antioxidants may be important, and the analyses cast no doubt on this. It would have been of interest to know whether the conclusions would have changed had total calories been omitted from the model.

(v) Although there is reasonably consistent evidence that dietary fat is positively related to lung cancer risk, the relative risks cited in this study in relation to saturated fat are really rather high, other epidemiological studies citing relative risks more of the order of two rather than six. Probably chance and some study design features have led to a high relative risk estimate in this study, and the true association is not actually as strong as this (see also the discussion on p1912 that the magnitude of the reported relative risk depends quite strongly on whether quintiles rather than quartiles are used, as some authors have done).

(vi) I note that many of the major components of saturated fat intake (hamburgers, cheeseburgers, hot dogs, ice cream, sausages) can be described as fast-food. They may reflect a particular type of personality or lifestyle. It should not be taken 100% that associations with dietary variables necessarily reflect effects of diet.

(vii) Although the difference between the saturated fat relative risks for adenocarcinoma and other lung cancers shown in Table 7 looks impressive, I note that the authors did not test it for statistical significance. The overall relative risk of 6.14 for highest/lowest quintile in Table 6 in fact is well within the 95% confidence limits for adenocarcinoma (3.77-34.4) and for other/unknown cell types (1.08-10.4) cited in Table 7. If

adenocarcinoma really is very strongly affected by saturated fat consumption, then Fontham's failure to take saturated fat into account in her ETS/lung cancer case-control study (see my reviews 567, 658) is an important omission.

(viii) The association of lung cancer risk with bean and pea consumption is only marginally statistically significant and the trend in relative risk by quintile not very impressive. In view of the number of endpoints studied, this is not strong evidence.

(ix) The association of lung cancer risk with citrus fruit and juice consumption is more strongly statistically significant. It is surprising inasmuch as it is anomalous with findings from other dietary studies. The study's failure to find a negative association generally with antioxidants such as β-carotene and vitamin C is also surprising. In the discussion the authors speculated that cases might have increased their consumption of citrus fruits and juices in an attempt to relieve symptoms of lung disease that had been present for a number of years. They also suggested that any beneficial effect of fruit and vegetable consumption might be limited to cancers that are more closely related to smoking, such as squamous-cell cancer. However they noted that the evidence from other studies was inconsistent in this respect and concluded that they had "no clear explanation" for their findings in relation to fruit and vegetable consumption.

(x) The authors did not take passive smoking into account in any analysis of dietary factors, because it did not affect risk estimates. This is unsurprising because passive smoking was not shown to be associated with risk of lung cancer. However this

should not be taken to indicate that confounding by diet is unimportant for the passive smoking/ETS relationship. No data are provided to allow the reader to judge whether, among controls, ETS exposed nonsmokers differed in dietary intake from nonsmokers not exposed to ETS. There may be a case for writing a letter to the journal asking Alavanja/Brownson for these data, and also how adjustment for their significant dietary factors affected ETS/lung cancer relative risk estimates.

Overall, while the study has some weaknesses and while there are some unexpected features of the findings, the Alavanja data are certainly consistent with the view that diet is a major determinant of risk of lung cancer in nonsmokers. If not taken into account, studies of ETS and lung cancer may produce importantly biased results. The likelihood of a role of dietary fat in lung cancer, emphasized by Ernest Wynder for some years, has been strengthened by this paper.

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